THE PREPARATION AND REACTIONS OF CERTAIN QUATERNARY AMMONIUM AND RELATED COMPOUNDS

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By

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INTRODUCTION

The need for compounds of good adrenergic blocking activity has been the object of extensive investigation in recent years. In order to get a better idea of the nature of adrenergic blocking activity, it might be best to understand first how an adrenergic compound functions.

Certain compounds like epinephrine or adrenaline, are powerful agents in stimulating the sympathetic nervous system, that part of the nervous system springing from the thoracic lumbar cord. The substance epinephrine is much like, if not identical to, the substance called sympathin, which is produced at the ending of a nerve in the smooth muscle or gland when a nerve is stimulated. Epinephrine and other adrenergic compounds accelerate the heart, constrict the muscles around the blood vessels which increases blood pressure, constrict the muscles of the spleen, thereby augmenting the number of circulating red blood cells, and release liver glycogen, which increases the blood sugar. This in many cases is a natural phenomenon and very important; for example, when an emergency arises after one is fatigued, it may give the energy and ability to preserve life. The accelerated pace of living in the past half century which has come about by the rise of the modern city with its business compexities, has been responsible to a considerable extent for the greatly increased number of cases of high blood pressure, heart conditions and the like. Because of this there has arisen a need for compounds of good adrenergic blocking activity which will enable one to neutralize or block the stimulating effect of these adrenergic compounds such as epinephrine and others.

There has been a marked interest recently in the N,N-disubstituted β-chloroethylamines as adrenergic blocking agents due largely to the discovery of N-(2-chloroethyl)-dibenzylamine, which is marketed under the trade name of "Dibenamine."

The adrenergic blocking activity of the β-chloroethylamine series appears to be dependent upon a number of factors, among which are molecular weight, electronegativity of the substituent groups, steric factors, solubility, and the toxicity of the substituent groups. Work published recently by Ullyot[1] and his co-workers would lead one to believe that in general, if the benzyl groups in N-(2-chloroethyl)-dibenzylamine are replaced with groups having a combined molecular weight exceeding that of the benzyl groups by too great a margin, decreased activity results. This work indicated that the activity was considerably less in N-(amyl-9-fluorenyl)-β-chloroethylamine hydrochloride than in either N-(ethyl-9-fluorenyl)-β-chloroethylamine hydrochloride or N-(2-chloroethyl)-dibenzylamine. Furthermore the compound with a normal heptyl group replacing the normal amyl group on the nitrogen was still less active. The work of Loew, Achenbach and Micetich[2] indicated that in the benzohydryl beta-chloroethylamine series, activity decreased when the third substituent was increased beyond secondary butyl. Other work by Loew and Micetich[3] indicated that in the N-(2-haloalkyl)-1-naphthylmethylamine derivatives, as the third substituent attached to the nitrogen increased in molecular weight, activity decreased. These workers stated that the ethyl derivatives were most active. Work by Gump and Nikawitz[4] indicated that changes in the electronic nature of the substituent groups affected the pharmacological activity considerably. They worked with compounds of the N-(2-chloroethyl)-dibenzylamine series, in which the hydrogen atoms were replaced by methyl groups in the ortho and para positions. Replacement of the hydrogens by methyl groups in the ortho and para positions resulted in a slower acting compound. Since the electron release or inductive effect of a methyl group is greater than that for hydrogen, it thereby increases the electron density on the nitrogen atom and perhaps changes the rate of formation of the ethyleneimonium structure. The presence of the methyl group in the meta position had apparently no effect on the activity of the compound. This would be expected since the effect of the methyl group would not be in conjugation with the resonance of the ring. Both of the effects are slight and the activity is not destroyed. When groups having greater electron release effect than methyl, such as ethyl and isopropyl, are placed in para position, activity is destroyed. These substituents have a greater electron release or greater inductive effect toward the ring, and thus give rise to a greater electron density at the nitrogen atom and increase the rate of formation of the ethyleneimonium structure to a considerable extent. When the hydrogen atoms were replaced by chlorine atoms in the ortho, or ortho and para positions, a decreased activity resulted. These ortho and/or para chlorine atoms, being strongly electronegative, would be expected to decrease the electron density around the nitrogen atom, thereby decreasing the rate of formation of the ethyleneimonium structure. With chlorine in the meta position, the compound retained slight activity. It would be expected that chlorine in the meta position would have only a slight effect and probably the reverse of that of an alkyl group.

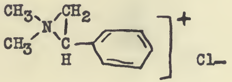
These same observations are also substantiated by the work of Nickerson[5] and Nickerson and Gump[6]. Results of experiments by Loew[2] and co-workers also gives evidence for the electronic effects in the benzohydryl series. These authors showed that the isopropyl and secondary butyl derivatives of the benzohydryl-β-chloroethylamine series are more active than the corresponding normal derivatives. These groups are likewise stronger electron-releasing groups than the corresponding normal groups.

Further work which bears out these electronic effects on the activity is that of Loew and Micetich[7,8]. These two men found 2-(2-biphenylyloxy)-2-chlorotriethylamine to be extremely active whereas 2-(3-biphenylyloxy)-2-chlorotriethylamine was inactive. The rate of formation of the ethyleneimonium structure is undoubtedly affected by the presence of the phenyl substituent in the meta position relative to the ether oxygen, rather than ortho, by eliminating the possibility of hyperconjugation, and changing the electron density around the nitrogen atoms. The compound 2-(2-cyclohexylylphenoxy)-2'-chlorotriethylamine was also found to be inactive which supports this argument.

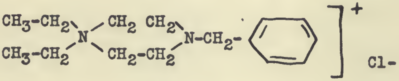
Evidence that steric factors are important is brought out in the work of Garbrecht, Hunter and Wright[9]. These workers prepared N-(B-chloroethyl)-2,3-dihydro-1-benz[de] isoquinoline hydrochloride and found it to be inactive. They found, by assembling the structure of this compound from Fisher-Hirschfelder models, that the nitrogen of this compound was held rigidly out of the plane of the naphthalene ring, whereas in N-(2-chloroethyl)-dibenzylamine hydrochloride the nitrogen atom could become planar with the phenyl rings by rotating about the carbon-carbon single bonds.

It appears from the above discussion that the rate of formation of the ethyleneimmonium structure is important. It also appears to be true from evidence cited above that this rate of formation must be maintained within certain narrow limits, since too great an increase or decrease in electron density around the nitrogen atom, as the result of the presence of electron releasing groups or electron attracting groups in the proper positions in the ring, results in less pronounced activity than in N-(2-chloroethyl)-dibenzylamine, the one used and marketed as "Dibenamine."

The rate of formation of the intermediate ethyleneimonium structure, and its ultimate stability, should be dependent upon the ease with which the β-chlorine is lost as a chloride ion, resulting in the formation of the carbonium ion, as well as upon the electron density around the nitrogen as controlled by inductive and hyperconjugation effects. A few compounds have been studied in which this effect has been observed. Nickerson and Gump[6] showed that the activity was destroyed when the halogen was of the vinyl halide type such as a 2-bromoallyl group linked to the nitrogen. Dibenzyl-2-bromoallyl amine was found to be inactive. The halogens of vinyl halides are held tightly and thus do not ionize to any appreciable extent. The reverse effect has also been observed by Nickerson and Gump[6] in the case of dibenzyl-β-chloro-β-phenylethylamine and by Hunt[10] in the case of dimethyl-β-chloro-β-phenylethylamine. Both of these compounds were found to be active. The β-chlorine is a typical benzyl chloride and would be expected to ionize readily because of the resonance in the benzyl structure which stabilizes the ion. The ethyleneimonium structure of the dimethyl derivatives is in reality a substituted benzyl amine as shown below.



It has also been shown by Nickerson and Gump[6] that replacement of one of the benzyl groups in N-(2-chloroethyl)-dibenzylamine by dibenzylaminoethyl or diethylaminoethyl groups results in loss of activity. This might perhaps be the result of the formation of a substituted piperazinium chloride of the following structure, rather than the ethyleneimonium structure, since the six membered ring is more probable than the three membered ring:

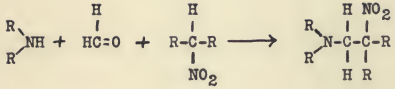


This type of ring closure has been observed to take place by Bartlett, Rose, and Swain[11] under certain conditions. These authors gave evidence for the formation of a dimer from only dimethyl-β-chloroethylamine.

The adrenergic blocking activity in clinical application is limited largely by the toxicity of the compound. Some of the compounds have activity of only short duration, while some like "Dibenamine" are capable of blocking certain adrenergic responses for a period of several days after a single dose.

According to Hunt[12] the success of the adrenergic blocking activity is ascribed to the formation of the highly reactive imine ring, under certain physiological conditions. This belief was substantiated by the fact that the blocking effect could be prevented by the prior administration of thiosulfate, an action which is attributed to the ability of this ion to combine with the imine form of such compounds with the production of an inactive ethyl thiosulfate derivative.

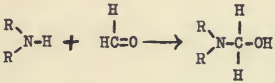
The similarity of the adrenergic blocking compounds to the quaternary ammonium salts obtained through the Mannich[13] reaction is of interest here, especially since considerable work along this line was already in progress in this laboratory. This reaction consists of the condensation of ammonia, a primary, secondary, or tertiary amine, usually in the form of the hydrochloride with formaldehyde and a compound with at least one hydrogen atom of pronounced reactivity. The active hydrogen for example, may be one of the alpha hydrogens adjacent to a carbonyl group, a carboxyl group, an ester linkage, phenolic hydroxyl, nitro, or other activating groups. The essential feature of this reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted amino methyl group, as shown by the following:



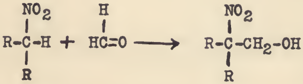
These compounds are usually referred to as Mannich bases because this type of condensation was first recognized as a general reaction by Mannich and his co-workers after he began a detailed study of it in 1917. However, examples of the reaction were observed by Henry[14] as early as 1895.

His work was initiated by the observation that antipyrine salicylate, formaldehyde, and ammonium chloride reacted to form a tertiary amine. Since aminopyrine failed to react, it was evident that the reaction involved the only active hydrogen, the one on carbon 4 of antipyrine.

The mechanism of the Mannich reaction has not been established. The addition of the amine to formaldehyde as shown below has been considered as a primary step. However, the fact has been shown by



Bodendorf and Koralewski[15] that in some cases the disubstituted aminomethanol, in reaction with a compound with an active hydrogen, gives a yield less than that obtained when the amine, formaldehyde, and the activated hydrogen compound are reacted. Another possibility is that the initial step in the reaction is the formation of the methylol derivative of the compound with the active hydrogen, for example:



$$\mathrm{R{-}\underset{R}{\overset{NO_2}{C}}{-}H} + \mathrm{\overset{H}{H}C{=}O} \longrightarrow \mathrm{R{-}\underset{R}{\overset{NO_2}{C}}{-}CH_2{-}OH}$$

Because of the large number of compounds that can be prepared in this manner, there needs to be considerably more investigation into the mechanism of this reaction.

In the light of the above discussion it was decided to synthesize certain compounds in which the tendency of the B-chlorine atom to ionize would be altered by the substitution of electron-attracting or electron-releasing groups on the β-Carbon, thereby controlling the rate of formation of the ethyleneimonium structure. The other end of the molecule might likewise be subjected to similar treatment by the substitution of electron-attracting and electron-releasing groups on the para position of substituted dibenzylamine type compounds. If this could be carried out and shown to be true, then perhaps many of the compounds previously prepared could have their activity restored by altering substituents at either or both ends of the molecule, and new adrenergic blocking compounds could be synthesized in an organized manner.

It was decided to synthesize a molecule in which one R group, the one with the chlorine intended for ionization would be an allyl type chlorine because of their ease of ionization observed in other reactions. Since dibenzylamine type compounds were the better adrenergic blocking compounds already known, it seemed advisable to use for the other two R groups, benzyl radicals, which would be used as the comparison. These could then be compared with di-para-chloro-benzyl radicals which would serve as the R groups with the electron-withdrawing power. It was decided to use the di-para-methoxybenzyl compound as the one with the electron-releasing ability.

The use of these three compounds in this investigation would produce a scientific approach to the idea of the ethyleneimonium structure formation, since the electron density on the nitrogen atom could be altered to greater or lesser degree by varying the substituents in the ortho and/or para and meta positions while holding the other R group constant. This might enable one to achieve a finer balance of the ethyleneimonium formation, since it is the author's belief that in previously prepared compounds, unsuccessful as adrenergic blockers, the electronic effects were too great in either direction to yield good adrenergic blocking activity in the compounds. Therefore the R group with the halogen could be altered while holding the various benzyl or substituted benzyl radicals constant and thus exhaust the series in a scientific way.

For the alteration of the R group containing the halogen, it was decided to react the various substituted dibenzylamines with 1,2-dichlorobutene-3 in order to get isomers of the other proposed compounds. Furthermore, this would place the halogen on a carbon to the nitrogen which would still enable the three-membered ring to be formed. The chlorine in this case would no longer be an allyl type halogen, but it would still be under the influence of a double bond nearby, which might perhaps cause it to ionize with greater ease than one in a saturated chain.

Some suggested work for the future would be the determination of the actual rate of ethyleneimonium formation. This would be valuable both from a commercial standpoint and from an academic viewpoint in that it would enable one to check the predicted effect of the various electron-releasing and electron-withdrawing groups with the actual effect.

Because of the similarity in structure of the adrenergic blocking compounds and the quaternary ammonium salts prepared through the Mannich reaction of nitroalkanes, a study of some of the reactions of these β-nitro compounds appeared to be in order. After the preparation of a number of N-(2-nitro-2-methylpropyl)-dialkylamines, their reactions with methyl iodide, benzyl chloride, allyl bromide, and ethyl iodide to produce the quaternary ammonium salts would be studied. It was also decided to investigate the products of decomposition of some of these N-(2-nitro-2-methylpropyl)-dialkylamines when they undergo pyrolysis. From an investigation of this type it might be possible to make a worthwhile contribution to the mechanism of the Mannich reaction.

EXPERIMENTAL

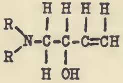
A. General Discussion

The compounds desired for starting materials, although they may seem to be somewhat common, were either very expensive or were no longer prepared commercially. Thus it was necessary to begin with more commonly occurring materials. In the di-para-chlorobenzyl series, the starting material was di-para-chlorobenzyl chloride which was obtained from the Matheson Company, and used as obtained. In the dibenzylamine series, the starting compound was dibenzylamine purchased from the Matheson Company. It was redistilled and the portion boiling at 156° at 10 mm. of Hg. pressure, was retained for use. The starting material for the para-methoxybenzyl series was para-methoxybenzyl alcohol which was also obtained from the Matheson Company. It was redistilled with a boiling point of 127-130° at 8 mm. of Hg. pressure. The 3,4-epoxybutene-1 was obtained from Eastman Kodak Company. It was redistilled with the boiling point recorded at 65°-8°. The 1,2-dichlorobutene-3 and the 1,4-dichlorobutene-2 were obtained from Carbide and Carbon Company. They were distilled before using. The boiling points were 123°, n_D^{26} 1.468 and 79° at 40 mm. of Hg. pressure, n_D^{23} 1.4844, respectively. The 2-nitropropane was purchased from Commercial Solvents Corporation, boiling point 120°. The various amines were purchased from Carbide and Carbon and were used as such. Other chemicals used were common laboratory reagents.

All temperatures are recorded in degrees centigrade and its symbol is omitted in conformity with present usage in scientific reports. Fractionations were accomplished by the use of a heated column 2 x 40 cm., packed with 1/4 inch Berl saddles, except those distillations in which the liquids boiled at very high temperatures. The higher boiling liquids were distilled through small claisen-type columns. Pyrex ground glass equipment and Glas-Col type heating mantles were used throughout. Pressures were measured by means of a Zimmerli gauge. Refractive indices were determined by an Abbe refractometer at 25°C. White light was used as the source of illumination. Analyses were done by the author if they were of the ionizable chloride type. Others were done by Rowland Laboratories[16] and Geller Microanalytical Laboratories[17].

The para-methoxybenzyl alcohol was converted to the chloride by the method of Quelet and Allard[18] in which an ethereal solution of para-methoxybenzyl alcohol, was added dropwise to concentrated hydrochloric acid in ether. The layers were separted and the para-methoxybenzyl chloride layer was dried and distilled. The para-methoxybenzyl chloride and the para-chlorobenzyl chloride were converted to their respective diamines by the method of Butler and

Benjamin[19]. In this method of preparation, the respective chlorides were added dropwise to an aqueous solution of ammonia and the temperature maintained at 75° for three hours. The lower oily layer was separated and distilled. The dibenzyl, the di-para-chlorobenzyl, and the di-para-methoxybenzylamines, respectively, were converted to the corresponding 1-di-substituted amino 2-hydroxy butene-3 derivatives



by the procedure of Kerwin, Ullyot, Fuson and Zirckle[20]. This involved reacting the amines with 3,4-epoxybutene-1 at 90-95°, and drying and distilling the product. The above disubstituted amino 2-hydroxy butene-3 compounds were converted to their corresponding hydrochlorides by dissolving them in ether and bubbling in gaseous hydrogen chloride. These compounds were then converted to the corresponding 2-chloro derivatives. This was accomplished through the use of thionyl chloride or phosphorus pentachloride.

Isomers of the 2-chloro compounds were prepared by reacting dibenzylamine and di-para-chlorobenzylamine with 1,2-dichlorobutene-3 for a number of hours on the steam bath while filtering off various fractions that were formed with time. They were finally obtained by precipitating them as the hydrochlorides after the other diamines had been precipitated and fractionally separated.

An attempt was made to prepare additional isomers by reacting dibenzylamine and di-para-chlorobenzylamine with 1,4-dichlorobutene-2 under similar conditions.

Several attempts were made to prepare 3,4-epoxybutene-1 by various methods since this compound has gone out of commercial production and was needed in this investigation. The method given by the literature[21] is a laborious process and produces a very poor yield.

The Mannich bases of the type N-(2-nitro-2-methylpropyl)-dialkylamines[22,23] were prepared by reacting the appropriate secondary amines with formaldehyde and 2-nitropropane. Most of the compounds studied were prepared from this nitro compound.

The N-(2-nitro-2-methylpropyl)-dialkylamines were each reacted with methyl iodide, benzyl chloride, allyl bromide and ethyl iodide at room temperature. The resulting products were then isolated, purified and identified. Following this, several of the above reactions were carried out at 120°, the reflux temperature of methyl isobutyl ketone.

The pyrolysis was carried out for N-(2-nitro-2-methylpropyl)-diethylamine hydrochloride, N-(2-nitro-2-methylpropyl)-piperidine hydrochloride and N-(2-nitro-2-methylpropyl)-morpholine hydrochloride, and the products of decomposition were identified.

The products from these reactions were in many cases very difficult to manipulate since they were gummy and tar-like as well as hygroscopic until they had been sufficiently purified by washing with various solvents such as acetone, alcohol, ether, methyl isobutyl ketone, ethylene dichloride, etc. This, of course, meant that in some cases a considerable amount of product was sacrificed for purity. In some cases it was not possible to isolate the compounds in a pure state.

B. Procedure

Preparation of para-methoxybenzyl chloride.

A mixture of 300 grams of concentrated hydrochloric acid and 300 ml. of ether was added to a 2 liter 3-necked ground glass flask fitted with a mechanical stirrer, a water cooled reflux condenser, and a dropping funnel. Then 185 grams (1.3 moles) of para-methyoxybenzyl alcohol dissolved in 300 milliliters of ether was added dropwise with vigorous stirring. The stirring was continued for about one-half hour after the alcohol-ether addition. The mixture was separated and the ether was removed from the product by evaporation on the steam bath. The last remaining amount was removed by the water pump. It was dried over Drierite for 24 hours and distilled. The boiling point of the para-methoxybenzyl chloride was 118° at 15 mm. Hg., and yielded 188 grams which was 89% of the theoretical amount. The para-methoxybenzyl chloride fumed in air.

Attempted preparation of para-methoxybenzyl chloride from methoxybenzene, formaldehyde, and gaseous hydrogen chloride[24]

To 555 grams of methoxybenzene (5.15 moles), 90 grams of 40% formaldehyde and 120 grams of anhydrous zinc chloride placed in a 2 liter 3-necked flask fitted with water-cooled reflux condenser, mechanical stirrer, thermometer, heating mantle, and gas addition tube, was added a rapid stream of gaseous hydrogen chloride along with hydrochloric acid. The mixture in the flask was heated to 60° before the addition of the hydrogen chloride, and was maintained at that temperature during the addition which took about 30 minutes. Heating at this temperature with stirring was continued for another hour. After cooling, the layer was separated, washed with sodium bicarbonate, dried over calcium chloride and distilled. In addition to recovered methoxybenzene, 60 grams of di-para-methoxyphenylmethane was obtained with a boiling point of 186° at 1 mm. Hg. pressure. It solidified upon cooling. Recrystallization from ethanol gave a melting point of 49°. A literature value by Beck[25] listed 48°-49° as the melting point for di-para-methoxyphenylmethane. It was expected that some of this would be formed since it was produced in lesser amounts in similar type reactions. No para-methoxybenzyl chloride was obtained.

Preparation of di-para-methoxybenzylamine

To a 1 liter 3-necked ground glass flask equipped with a water-cooled reflux condenser, mechanical stirrer, thermometer, heating mantle, and dropping funnel was added 170 grams (0.55 mole equivalent) of para-methoxybenzyl chloride in a dropwise manner to an aqueous solution of 134.2 grams (1.1 mole equivalent) of ammonium hydroxide (28% ammonia) diluted with 515 grams of water. The ammonia solution was heated to 75° before addition was begun and it was maintained at that temperature throughout the addition of the para-methoxybenzyl chloride. After the addition of the para-methoxybenzyl chloride, the mixture was heated at 75° with continuous stirring for three hours. After cooling, the oily lower layer was separated, and it was noticed that it solidified within several hours. It was then stirred with 3 normal hydrochloric acid to convert the various amines to their hydrochlorides. The mushy mixture was heated on the steam bath to promote complete conversion, and the hydrochloric acid solution was decanted off. The solid product was then heated with hot sodium hydroxide on the steam bath for 2 days. After the oily amine layer had separated, it appeared that some of the hydrochloride had not been completely changed to the free amine. Thus it was stirred with ether to take up the free amines. The ether layer was separated, evaporated on the steam bath, dried for several days over potassium hydroxide and distilled. The boiling point was recorded at 175°-180° at 1 mm. of Hg. pressure. A yield of 48 grams, 34% of the theoretical amount was obtained. A white solid remained in the distilling pot. The hydrochloride of the di-para-methoxybenzyl amine was prepared by dissolving the amine in ether and precipitating it by bubbling gaseous hydrogen chloride through. The hydrochloride was recrystallized three times from ethanol. The melting point was 240°- 241°. The literature value[26] recorded for the hydrochloride of dianisylamine (di-para-methoxybenzyl amine) is 243°-244°.

Preparation of di-(para-chloro)-benzylamine

A mixture of 137 grams of commercial ammonium hydroxide containing 28% ammonia (2.3 mole) was diluted with 525 grams of water and placed in a 1 liter 3-necked flask equipped with a mechanical stirrer, water-cooled reflux condenser, heating mantle, thermometer and dropping funnel. The solution was heated to 75° and then 161 grams (0.5 mole) of para-chlorobenzyl chloride was added dropwise. The ratio was intended to be one mole of the halide to 4.5 moles of ammonia. After the addition, the mixture was maintained at 75° with constant stirring for about 3.5 hours. After cooling the oily lower layer was separated, and dilute hydrochloric acid was added with stirring. A day later, after it was believed to have been completely converted to the hydrochloride, it was heated with about 400 milliliters of ethanol to dissolve the unreacted para-chlorobenzyl chloride to prevent further reaction with the di-(para-chloro)-benzylamine to form the tertiary amine during the distillation. Also the hot alcohol dissolved out most of the mono-para-chlorobenzylamine. The di-para-chlorobenzylamine hydrochloride was heated on the steam bath with concentrated sodium hydroxide for approximately 24 hours since the free amine was difficult to liberate. The oil that separated was dried over potassium hydroxide and distilled with a boiling point of 174°-176° at 1 mm. of Hg. pressure. A yield of 37 grams of the colorless liquid was obtained which was 27.8% of the theoretical. It must be taken into consideration that quite a little loss occurred in the washing of the hydrochloride with the ethanol to remove unused para-chlorobenzyl chloride and the mono-para-chlorobenzylamine. The hydrochloride of the di-(para-chloro)-benzylamine was prepared by dissolving it in ether and passing gaseous hydrogen chloride through. The di-(para-chloro)-benzylamine hydrochloride was recrystallized from methanol (quite insoluble in ethanol) three times and gave a melting point of 287-9°. This checked with that recorded in the literature of 286-8°. The picrate was also prepared of the di-(para-chloro)-benzylamine. The melting point was 191° compared with 187° by Winnan[27]. Analysis for di-(para-chloro)-benzylamine: Calc'd: 11.80% Cl. Found: 12.06% Cl.

In one run of this preparation in which the para-chlorobenzyl chloride was not washed out with ethanol, only unused para-chlorobenzyl chloride was obtained upon distillation with a very high boiling fraction remaining. After cooling the distilling vessel, solidification took place. Several recrystallizations of this white solid gave a melting point of 79°. The hydrochloride melted at 192°. The compound was shown to be the hydrochloride of tri-para-chlorobenzylamine from the analysis, and was produced in good yield.

Analysis:	Calculated		Found	
	Chlorine	33.20%	Chlorine	32.97%
	Nitrogen	3.27%	Nitrogen	3.14%

Preparation of 1-dibenzylamino-2-hydroxy butene-3

To 98.5 grams (0.5 mole) of dibenzylamine in a 300 milliliter 3-necked flask fitted with a mechanical stirrer, water-cooled reflux condenser, thermometer, and heating mantle, was added 35.0 grams (0.5 mole) of 3,4-epoxybutene-1. The solution was heated to 90°-95° with stirring for 4 hours, during which time a considerable amount had time to react. The temperature was then elevated to 140° for two additional hours with continued stirring. It was then cooled, dried over Drierite, and distilled at 190°-196° at 6 mm. of Hg. pressure. A yield of 30 grams of a yellow oil was obtained which was 25% of the theoretical. The hydrochloride was prepared of the 1-dibenzylamino-2-hydroxy butene-3 by dissolving it in benzene (it gives a somewhat more gummy and hygroscopic solid if precipitated from ether) and passing gaseous hydrogen chloride through it. A red oil separated which solidified after several hours. It was recrystallized three times from methyl isobutyl ketone after washing with acetone, to give a snowy white solid. This material was not hygroscopic as reported in the literature; however, the melting point of 157°-158° was the same as that reported in the literature.

Preparation of 1-di-(para-methoxybenzyl) amino-2-hydroxy butene-3

A quantity of 42 grams, (0.16 mole) of di-(para-methoxy)-benzylamine was placed in a flask fitted with a water-cooled reflux condenser, mechanical stirrer, thermometer, and heating mantle. To this was added 12 grams, (0.16 mole) of 3,4-epoxybutene-1, and the mixture was heated at 95° for 4 hours. After this time the refluxing of the 3,4-epoxybutene-1 had slowed down considerably. The temperature was gradually increased to 140° as the refluxing of the epoxybutene would allow. After the temperature had reached 140°, it was maintained there for an additional

2 hours, making a total of 10 hours of heating. The compound was dried over Drierite and distilled with the boiling point recorded at 158°-188° at 1 mm. of Hg. pressure. The product was a very viscous yellow oil. A yield of 24 grams, 45% of the theoretical was obtained. The hydrochloride was prepared of the 1-di-(para-methoxybenzyl) amino-2-hydroxy butene-3 by dissolving in ether and passing gaseous hydrogen chloride through. A viscous syrupy substance separated out on the bottom and the walls of the Erlenmeyer flask container. A couple of days later the material turned crystalline. After considerable trouble it was finally recrystallized from methyl isobutyl ketone with a melting point of 162°-163°.

The compound was analyzed for chlorine:

Calculated: 9.80%
Found : 10.11%

Preparation of 1-di-(para-chlorobenzyl) amino-2-hydroxy butene-3

To 74 grams (0.28 mole) of di-(para-chlorobenzyl) amine placed in a 300 milliliter 3-necked flask fitted with mechanical stirrer, a water-cooled reflux condenser, thermometer, and heating mantle, was added 19.6 grams (0.28 mole) of 3,4-epoxybutene-1. The mixture was heated at 95° for 4 hours and then the temperature was raised gradually to 140° where it was maintained for an additional 2 hours.

The total time was 7 hours. The mixture was cooled, dried over Drierite and distilled with a recorded temperature of 195^{o}-210^{o} at 1 mm. of Hg. pressure. The yield, 23 grams of yellow oil, was 24% of the theoretical amount. The hydrochloride was prepared of the 1-di-(para-chlorobenzyl) amino-2-hydroxy butene-3 by dissolving it in ether and passing gaseous hydrogen chloride through. It was recrystallized 3 times from ethanol, giving a melting point of 196°-198°. The 1-di-(para-chlorobenzyl) amino-2-hydroxy butene-3 was too insoluble to be recrystallized from the methyl isobutyl ketone as were the other two in this series. It was quite insoluble in ethanol.

Analysis:	Calculated		Found	
	Chlorine	28.60%	Chlorine	28.98%
	Nitrogen	3.76%	Nitrogen	3.81%

Preparation of 1-dibenzylamino-2-chlorobutene-3 hydrochloride

To 4 grams (approximately 0.01 mole) of recrystallized 1-dibenzylamino-2-hydroxybutene-3 hydrochloride of good melting point, placed in a small Erlenmeyer flask, was added 25 milliliters of chloroform. To this, 2 grams (0.02 mole) of redistilled thionyl chloride was added dropwise and slowly with ice cooling of the mixture, as there was an appreciable amount of heat of reaction. The addition was regulated by the increase of temperature from the heat of reaction as the solution reached the boiling point after the addition of only a few drops. After the thionyl chloride was added and the reaction had subsided, it was heated on the steam bath for 10 minutes. Then, the mixture was cooled, evaporated at the water pump and then evacuated for a couple of days in a vacuum desiccator. The gummy residue was then given a quick washing with methyl isobutyl ketone to remove some of the gummy material. After considerable difficulty it was finally recrystallized from ethanol, giving a white solid with a melting point of 258°-259°. One gram of product was obtained.

Analysis:	Calculated		Found	
	Chlorine	21.98%	Chlorine	21.11%
	Nitrogen	4.34%	Nitrogen	4.32%

The 1-dibenzylamino-2-chlorobutene-3 hydrochloride was also prepared by dissolving the amino alcohol hydrochloride in chloroform and adding phosphorus pentachloride. The details were the same as in the above description. The compound was recrystallized from ethanol, giving a melting point of 258°-259°. A mixed melting point with the product formed from thionyl chloride gave no change in the melting point. The compounds were assumed to be the same.

Attempted preparation of 1-di-(para-chlorobenzyl) amino-2-chlorobutene-3-hydrochloride

To 11.5 grams (0.03 mole) of recrystallized 1-di-(para-chlorobenzyl) amino-2-hydroxybutene-3 hydrochloride of good melting point placed in an Erlenmeyer flask, was added 25 milliliters of chloroform. To this, 9.2 grams (0.07 mole) of redistilled thionyl chloride was added. The thionyl chloride was added dropwise and slowly while the solution was cooled with ice. The addition of the thionyl chloride was regulated by the increase of temperature from the heat of reaction since the reaction was highly exothermic. After the reaction had subsided, it was heated on the steam bath for 15 minutes. The mixture was cooled, evaporated at the water pump and then evacuated for 2 days in a vacuum desiccator. Methyl isobutyl ketone was added to the gummy residue and then it was allowed to stand for about 10 days when a fair amount of amorphous substance had formed on the surface. The solvent and the tan amorphous substance was decanted, filtered off and recrystallized from ethanol three times. There being no change in the melting poing after the second and third recrystallization, the melting point was recorded as 168°-170°. Four grams of product were obtained.

Analysis:	Calculated		Found	
	Chlorine	36.24%	Chlorine	51.71%
	Nitrogen	3.58%	Nitrogen	5.97%

Preparation of the 1-di-(para-chlorobenzyl) amino-2-hydroxy butene-3 hydrochloride was accomplished in a similar manner by adding phosphorus pentachloride to the amino-alcohol hydrochloride dissolved in chloroform. The chloroform was evaporated, the residue washed with methyl isobutyl ketone, and recrystallized from ethanol.

Attempted preparation of 1-di-(para-methoxybenzyl) amino-2-chlorobutene-3 hydrochloride

To 6.7 grams (0.02 mole) of recrystallized 1-di-(para-methoxybenzyl) amino-2 hydroxybutene-3 hydrochloride of good melting point placed in an Erlenmeyer flask, was added 25 milliliters of chloroform. To this, 4.8 grams (0.04 mole) of redistilled thionyl chloride was added dropwise and slowly to the ice-cooled solution. The rate of addition was determined by the heating effect from the heat of reaction. After the addition, and when the solution had cooled, it was heated for 10 minutes on the steam bath. The mixture was cooled, evaporated at the water pump and placed in a vacuum desiccator. The gummy residue was evacuated at various times while stored in a vacuum desiccator.

A number of runs were tried under various conditions, with evacuation for extended periods. Various solvents were tried to extract the gummy material. A few drops of pyridine were added as a catalyst, and similar trials with phosphorus pentachloride were run with no success.

Attempted preparation of 1-chloro-2-dibenzylamino butene-3 hydrochloride

A quantity of 20 grams (0.10 mole) of dibenzylamine was placed in an Erlenmeyer flask of 125 milliliter capacity containing 30 milliliters of benzene. Then 6.5 grams (0.05 mole) of 1,2-dichlorobutene-3 was added. The flask was fitted with a rubber stopper and air condenser and placed on the steam bath. The dibenzylamine was added in twice the molar quantity because it had been previously discovered that the dibenzylamine was a stronger base than the expected product, 1-chloro-2-dibenzylamino butene-3. After several hours of heating the crystals were removed by filteration. This was continued at intervals until the equivalent quantity of dibenzylamine hydrochloride was obtained. The various fractions removed by filteration were recrystallized from ethanol and analyzed in an attempt to locate the new compound. The mixture was then cooled, and gaseous hydrogen chloride passed into it. This precipitated any remaining dibenzylamine as the hydrochloride and the hydrochloride of the 1-chloro-2-dibenzylamino butene-3. The new hydrochloride was insoluble in ethanol, so methanol was used for recrystallization. The white solid had a melting point of 252°-253°. A mixed melting point with dibenzylamine hydrochloride from the earlier fractions gave a lowering of the melting point of about 10°. By analysis it was shown to be 1,2-di-(benzylamino) butene-3 dihydrochloride, or an isomer of this compound.

Analysis of the compound:

Calculated		Found	
Chlorine	13.65%	Chlorine	13.66%
Nitrogen	5.41%	Nitrogen	5.27%

Previous attempts included a run using sodium bicarbonate to take up the liberated hydrogen chloride, but this was unsuccessful. Another attempt included the use of twice the molar quantity of piperidine to take up the liberated hydrogen chloride, the reaction being carried out in the same manner as described above. The first crystals removed by filteration were piperidine hydrochloride. It was identified by the melting point of 245°, the same as recorded for piperidine hydrochloride. An analysis gave 29.24% chlorine as compared to a theoretical value of 29.20%. Then hydrogen chloride was bubbled through the remaining solution precipitating a white compound which when recrystallized from ethanol had a melting point of 313°-315°. The compound on analysis was shown to be the 1,2-diperidino butene-3 hydrochloride, or an isomer of this compound.

Analysis of the compound:

Calculated		Found	
Chlorine	24.01%	Chlorine	24.06%

Preparation of 1-chloro-2-di-(para-chlorobenzyl) aminobutene-3 hydrochloride

To 26.6 grams (0.1 mole) of di-(para-chlorobenzyl) amine in an Erlenmeyer flask of 125 milliliter capacity, fitted with a rubber stopper and air condenser was added 30 milliliters of benzene. Then 6.5 grams (0.05 mole) of 1,2-di-chlorobutene-3 was added and the flask was placed on the steam bath. Crystal formation began immediately. After several hours of heating, the crystals were removed by filteration and recrystallized. Less product had been formed after this time than with the dibenzylamine in the analogous reaction. This procedure was continued for several days until approximately an equivalent quantity of di-(para-chlorobenzyl) amine hydrochloride had been formed and little further crystal formation occurred. The solution was then cooled and gaseous hydrogen chloride passed through. This precipitated any remaining di-(para-chlorobenzyl amine and the hydrochloride of the expected 1-chloro-2-di-(para-chlorobenzyl) aminobutene-3. The hydrochloride was recrystallized from methanol. The melting point was 286° with darkening before melting. A mixed melting point with di-para-chlorobenzylamine hydrochloride gave a lowered melting point.

Analysis of the compound:

Calculated		Found	
Chlorine	36.24%	Chlorine	34.36%
Nitrogen	4.26%	Nitrogen	4.32%

The compound was not what was expected. Although the per cent nitrogen is accurate, the per cent chlorine is exactly midway between the values of the mono and di derivatives of the butene compound.

Attempted synthesis of 3,4-epoxybutene-1 from 1,2-dichlorobutene-3

A fifty per cent solution of sodium hydroxide containing 100 grams (2.5 moles) of sodium hydroxide was added to a 500 ml. 3-necked ground glass flask fitted with mechanical stirrer, water-cooled reflux condenser, thermometer, heating mantle, and dropping funnel on a side arm attached to a water-cooled condenser. Then 62 grams (0.5 mole) of 1,2-dichlorobutene-3 was added dropwise to the solution of sodium hydroxide heated to 115°. The temperature was maintained here because 1,2-dichlorobutene-3 boils at 123°. In about 15 minutes a distillate of oil and water began to come over. Distillation was continued for about an hour, after which the lower oily layer was separated, dried over Drierite and fractionated at atmospheric pressure. A liquid which boiled at 58°-59° was obtained in a yield of 10 grams, as well as a recovery of 30 grams of

1,2-dichlorobutene-3. The reaction product had index of refraction of 1.45. The boiling point and index of refraction were the same as that recorded for Chloroprene, and after a few days the product had polymerized to Neoprene rubber. The product represented a 12% yield of chloroprene. About 5 grams of a yellow solid was filtered out of the reaction vessel but identification was unsuccessful.

A number of runs were tried at various temperatures and with various concentrations of sodium hydroxide. No 3,4-epoxybutene-1 was obtained.

Attempted synthesis of 3,4-epoxybutene-1 from 1,2-dichlorobutene-3 and sodium acetate

A quantity of 62 grams (0.5 mole) of 1,2-dichlorobutene-3 was placed in a 500 milliliter flask fitted with mechanical stirrer, thermometer, water-cooled reflux condenser, heating mantle, and a dropping funnel. Then 41 grams (0.5 mole) of sodium acetate was dissolved in 100 milliliters of water and added dropwise to the 1,2-dichlorobutene-3 heated at 85°. The heating and stirring was continued for three days (72 hours). The layers were separated with a separatory funnel, after long standing as the layers separated slowly. The oily layer was dried over Drierite and distilled. In addition to recovered 1,2-dichlorobutene-3, about 4 milliliters of a straw-colored liquid which boiled at 129° was obtained. The index of refraction was 1.4430 as compared to 1.45 for the original material. The product was not further identified.

A number of variations of this above procedure were tried varying the temperature of reaction and the concentration of the sodium acetate with no success.

Preparation of N-(2-nitro-2-methylpropyl)-diethylamine

A quantity of 270 grams (3 moles) of 2-nitropropane and 180 milliliters of dioxane were placed in a 3 liter 3-necked flask fitted with a water-cooled reflux condenser, mechanical stirrer, thermometer, heating mantle, and dropping funnel. Then 219 grams (3.0 moles) of diethylamine dissolved in 360 grams of dioxane were added and the mixture was cooled to 5°. Next 60 milliliters of 2% sodium hydroxide was added with the temperature kept below 10°. Finally 252 grams of 40% aqueous formaldehyde was added dropwise through the dropping funnel with the temperature kept below 10°. The ice bath was then removed and stirring continued for one hour. The reaction was heated to 88°-90° (reflux temperature) with stirring for three hours. The mixture was cooled and 1200 milliliters of cold water was added with good stirring. It was allowed to stand for the layers to separate. The product was removed, dried over Drierite and distilled with a boiling point of 87° at 10 mm. of Hg pressure.

The hydrochloride of the N-(2-nitro-2-methlpropyl)-diethylamine was prepared by dissolving the amine in ether and by precipitating with gaseous hydrogen chloride. It was recrystallized from methyl isobutyl ketone, with melting point of 142°-144°.

Analysis:	Calculated	Found
	Chlorine 16.83%	Chlorine 16.85%

By a similar procedure N-(2-nitro-2-methylpropyl)-dipropylamine, N-(2-nitro-2-methylpropyl)-dibutylamine, N-(2-nitro-2-methylpropyl)-diallylamine, N-(2-nitro-2-methylpropyl)-piperidine, and N-(2-nitro-2-methylpropyl)-morpholine were prepared.

Reaction of N-(2-nitro-2-methylpropyl)-diethylamine with methyl iodide

A quantity of 8.7 grams (0.05 mole) of N-(2-nitro-2-methylpropyl)-diethylamine was added to a test tube. To this was added 7.1 grams (0.05 mole) of methyl iodide. This was allowed to stand for several months after which an appreciable amount of compound formation had occurred. The compound was recrystallized from amyl alcohol three times and dried in a vacuum desiccator for two days. The melting point of the white to tan-like powder remained the same after the second and third recrystallization with a temperature of 171°-172°. The analysis of the compound for ionizable iodide showed the compound to be the methyl quaternary ammonium iodide of the starting amine. The analysis was determined by dissolving the sample in water and titrating with silver nitrate.

Analysis:	Calculated	Found
	Iodide 40.20%	Iodide 40.41%

Similar reactions were carried out for N-(2-nitro-2-methylpropyl)-piperidine, N-(2-nitro-2-methylpropyl)-morpholine, N-(2-nitro-2-methylpropyl)-dipropylamine, N-(2-nitro-2-methylpropyl)-dibutylamine and N-(2-nitro-2-methylpropyl)-diallylamine by adding equivalent molar quantities of the two compounds in test tubes. In the following, only the recrystallizing solvent, the melting point, the analysis, and the description of the hydrochloride formed will be given.

For N-(2-nitro-2-methylpropyl)-piperidine with methyl iodide: The compound was recrystallized from amyl alcohol. The melting point was 208°-209°. Compound was shown to be the methyl quaternary ammonium iodide of the starting amine.

Analysis:	Calculated	Found
	Iodide 38.69%	Iodide 38.81%

For N-(2-nitro-2-methylpropyl)-morpholine with methyl iodide: The compound was recrystallized from water. The melting point was 195°-196°. The compound, a white solid, was shown to be the methyl quaternary ammonium iodide of the starting amine.

Analysis:	Calculated	Found
	Iodide 38.43%	Iodide 38.75%

For N-(2-nitro-2-methylpropyl)-diallylamine: The white compound was recrystallized from ethanol. The melting point was 104.0°. The compound was shown to be the methyl quaternary ammonium iodide of the starting amine.

Analysis:	Calculated	Found
	Iodide 37.31%	Iodide 37.47%

Reaction of N-(2-nitro-2-methylpropyl)-diethylamine with benzyl chloride

A quantity of 8.7 grams (0.05 mole) of N-(2-nitro-2-methylpropyl)-diethylamine was added to a test tube. To this was added 6.6 grams (0.05 mole) of benzyl chloride. This was allowed to stand for several months, after which time a considerable amount of compound formation had taken place. The product was recrystallized from amyl alcohol, giving a melting point of 193°, after drying for two days in a vacuum desiccator. The melting point remained the same after two recrystallizations. The analysis of the white compound for ionizable chloride showed the compound to be benzyl diethylamine hydrochloride. Thus the 2-nitro-2-methylpropyl group had split off.

Analysis:	Calculated	Found
	Chloride 17.79%	Chloride 17.84%

Similar reactions were carried out with N-(2-nitro-

2-methylpropyl)-piperidine, N-(2-nitro-2-methylpropyl)-morpholine, N-(2-nitro-2-methylpropyl)-dipropylamine, N-(2-nitro-2-methylpropyl)-dibutylamine and N-(2-nitro-2-methylpropyl)-diallylamine, by adding equivalent quantities of benzyl chloride to each in test tubes. In the following, only the recrystallizing solvents, the melting point, the analysis and the description of the compound formed will be given.

For N-(2-nitro-2-methylpropyl)-piperidine: The compound was recrystallized from ethyl alcohol. The melting point was 183°. The slightly tan solid was shown to be benzyl piperidine hydrochloride.

Analysis:	Calculated	Found
	Chloride 16.70%	Chloride 16.30%

For N-(2-nitro-2-methylpropyl)-morpholine: The compound was recrystallized from ethanol. The melting point was 248°. The white crystalline solid was benzylmorpholine hydrochloride.

Analysis:	Calculated	Found
	Chloride 16.62%	Chloride 16.44%

Reaction of N-(2-nitro-2-methylpropyl)-diethylamine with allyl bromide

To 8.7 grams (0.05 mole) of N-(2-nitro-2-methylpropyl)-diethylamine in a test tube was added 6.1 grams (0.05 mole) of allyl bromide. This was allowed to stand for several months until an appreciable amount of compound formation had taken place. The solid was quite resinous and was washed with amyl alcohol to remove the viscous material. It was recrystallized from amyl alcohol after considerable difficulty in removing the tarry-like material. The melting point was 133°. The analysis showed the compound to be the hydrobromide of the starting N-(2-nitro-2-methylpropyl)-diethylamine.

Analysis:	Calculated	Found
	Bromide 31.40%	Bromide 31.62%

Similar reactions were carried out with N-(2-nitro-2-methylpropyl)-piperidine, N-(2-nitro-2-methylpropyl)-morpholine, N-(2-nitro-2-methylpropyl)-dibutylamine, N-(2-nitro-2-methylpropyl)-dipropylamine and N-(2-nitro-2-methylpropyl)-diallylamine by adding equimolar quantities of allyl bromide to them in test tubes. In the following, only the recrystallizing solvent, the melting point, the analysis, and the description of the compound formed will be given. All of these compounds caused extreme difficulty in obtaining the crystals as they were hygroscopic until most of the impurities were removed.

For N-(2-nitro-2-methylpropyl)-piperidine: The solid which was quite tarry-like, was washed first with acetone to remove the viscous material, then was recrystallized from ethyl alcohol. The melting point of the slightly tan solid was 183°. Analysis showed the compound to be the hydrobromide of the starting N-(2-nitro-2-methyl propyl)-piperidine.

Analysis:	Calculated	Found
	Bromide 29.92%	Bromide 30.18%

For N-(2-nitro-2-methylpropyl)-morpholine: The compound was recrystallized from ethanol. The melting point of the white crystals was 177°. Analysis showed the compound to be the hydrobromide of the starting material.

Analysis:	Calculated	Found
	Bromide 29.85%	Bromide 30.38%

For N-(2-nitro-2-methylpropyl)-dibutylamine: The compound was filtered from the resinous material, dissolved in ethanol, and precipitated by adding dry ether. Then it was recrystallized from ethanol, with a melting point of 286°-288°. The white crystalline solid was found to be dibutylamine hydrobromide from analysis.

Analysis:	Calculated	Found
	Bromide 40.60%	Bromide 40.42%

For N-(2-nitro-2-methylpropyl)-dipropylamine: This compound again, as the one above, was difficult to work with, but was finally recrystallized from ethanol, giving a melting point of 267°-269° for the white crystalline solid. Analysis showed the compound to be the hydrobromide of dipropylamine. The melting point recorded in the literature for this compound is 271°.

Analysis:	Calculated	Found
	Bromide 43.92%	Bromide 44.30%

No crystalline solid could be obtained from the N-(2-nitro-2-methylpropyl)-diallyl amine. This is not surprising considering the difficulty encountered by Goette[28] and Bunch[29] in obtaining crystals from the pure di- and triallylamines and hydrogen bromide.

Reaction of N-(2-nitro-2-methylpropyl)-piperidine with ethyl iodide

To 8.5 grams (0.05 mole) of N-(2-nitro-2-methylpropyl)-piperidine in a test tube, was added 7.8 grams (0.05 mole) of ethyl iodide. This was allowed to stand for several months until a considerable amount of compound formation had taken place. The resinous material was removed by filteration, washed with cold ethanol, then recrystallized from ethanol. The melting point of the white crystalline material was 158^{o}-159^{o}. Analysis showed the compound to be the hydroiodide of the starting N-(2-nitro-2-methylpropyl)-piperidine.

Analysis:	Calculation	Found
	Iodide 40.40%	Iodide 40.65%

Reaction of N-(2-nitro-2-methylpropyl)-diethylamine and benzylchloride with heat

To 87 grams (0.5 mole) of N-(2-nitro-2-methylpropyl)-diethylamine in 150 grams of methyl isobutyl ketone was added 63 grams (0.5 mole) of benzyl chloride. The mixture was placed in a 500 milliliter flask fitted with a sealed mechanical stirrer, water-cooled reflux condenser, a heating mantle, and side arm with cold trap. The mixture was heated at 123° (the reflux temperature of the solvent) for five hours. The solid compound was filtered and recrystallized. The melting point was 193°, same as that for benzyl diethylamine hydrochloride. Mixed melting points and analysis showed it to be the hydrochloride of benzyl diethylamine, the same as that obtained by prolonged reaction at room temperature.

Analysis:	Calculated	Found
	Chloride 17.79%	Chloride 18.81%

In an effort to identify the other products of the reaction, the filtrate was dried over Drierite and distilled, yielding methyl isobutyl ketone and a small amount of 2-nitropropane. The expected product of the reaction, 2-nitropropene, was not obtained.

During the course of the reaction, a solid was noticed to have formed on the walls of the flask after approximately an hour of heating and gradually accumulated. After another hour and a half to two hours it disappeared completely. A second run was made and the solid was filtered and recrystallized from ethylene dichloride. It gave a melting point of 226°-227°. A mixed melting point with diethylamine hydrochloride, and analysis showed it to be diethylamine hydrochloride.

Analysis:	Calculated	Found
	Chloride 32.35%	Chloride 32.34%

Equimolar quantities of diethylamine hydrochloride and benzyl chloride were heated under identical conditions with methyl isobutyl ketone in an effort to determine whether or not the benzyl diethylamine hydrochloride was formed from these two compounds in the above reaction. Since no benzyl diethylamine hydrochloride was obtained in this reaction, obviously this compound was obtained above through some other mechanism.

Reaction of N-(2-nitro-2-methylpropyl)-piperidine and benzyl chloride with heat

The reaction was carried out the same as for N-(2-nitro-2-methylpropyl)-diethylamine with 93 grams (0.5 mole) of the amine and 63.2 grams (0.5 mole) of benzyl chloride. Benzyl piperidine hydrochloride was obtained as shown by the melting point of 183° and from the analysis. This same compound was obtained by prolonged reaction at room temperature.

Analysis:	Calculated	Found
	Chloride 16.70%	Chloride 16.35%

Reaction of N-(2-nitro-2-methylpropyl)-morpholine and benzyl chloride with heat

The reaction was carried out the same as for

N-(2-nitro-2-methylpropyl)-diethylamine, with 94 grams (0.45 mole) and 63 grams (0.5 mole) of benzyl chloride.

Benzyl morpholine hydrochloride was the product obtained as shown by the melting point of 244°-246° and from the analysis. The same compound was obtained without heat as previously described.

Analysis:	Calculated	Found
	Chloride 16.59%	Chloride 16.59%

Pyrolysis of N-(2-nitro-2-methylpropyl)-diethylamine hydrochloride

The hydrochloride salt was prepared by passing gaseous hydrogen chloride through an ethereal solution of N-(2-nitro-2-methylpropyl)-diethylamine. It was filtered and dried in a vacuum desiccator. The melting point was 142°-144°. A weight of 95.4 grams (0.454 mole) of the hydrochloride was placed in a round bottom 300 milliliter one-necked thermometer well flask, fitted with thermometer, heating mantle, Claisen distilling head with water-cooled condenser, receiver, and vacuum take-off with cold trap. A safety shield was placed in front of the apparatus before proceeding.

The pressure was reduced to 10 millimeters of Hg., and heating was begun. The pyrolysis started at 100° and the temperature was maintained there for about an hour and then the temperature was gradually increased to 200° at which time pyrolysis appeared to be complete. The time was about five hours. The liquid distilled and condensed in the dry ice-acetone trap. The color of the liquid was a deep blue, about the color of the copper-ammonia complex ion. The liquid was taken out, separated from the water, (5 milliliters) washed with hydrochloric acid, which turned the color pale yellow, dried over Drierite, and distilled at atmospheric pressure. The boiling point was 119.5°. Index of refraction was 1.3910 at 29°. The compound was identified as 2-nitropropane, and a yield of 30 grams, 74.3% of the theoretical was obtained. Proof of identity of 2-nitropropane is given below:

2-Nitropropane: index of refraction at 29°: 1.3910; boiling point: 119.5°.

Compound obtained: index of refraction at 29°: 1.3910; boiling point: 119.5°. Infrared curves were run on this compound and 2-nitropropane. The curves were identical.

Water was put into the reaction flask with the charred mass and allowed to stand overnight to dissolve the other product. The next day the water was filtered and evaporated on the steam bath. A quantity of 23 grams of diethylamine hydrochloride was recrystallized from the residue giving 48% of the theoretical yield. The recrystallizing solvent was ethanol. The melting point was 224°, the same as for diethylamine hydrochloride.

Analysis:	Calculated	Found
	Chloride 32.35%	Chloride 32.40%

The products obtained were 2-nitropropane, diethylamine hydrochloride, water, and probably carbon dioxide.

Pyrolysis of N-(2-nitro-2-methylpropyl)-piperidine hydrochloride

The hydrochloride salt was prepared by passing gaseous hydrogen chloride through an ethereal solution of N-(2-nitro-2-methylpropyl)-piperidine. The salt was filtered and dried in a vacuum desiccator. The melting point was 183°. A quantity of 103 grams (0.465 mole) of the hydrochloride was placed in a 300 milliliter round-bottom, one-necked, thermometer well flask, fitted with thermometer, heating mantle, Claisen distilling head with water-cooled condenser, receiver and vacuum take-off with cold trap. A safety shield was placed in front of the apparatus before proceeding.

The pressure was reduced to 10 millimeters of Hg pressure and heating was started. The temperature was elevated slowly. The pyrolysis appeared to begin around 100° and the temperature was elevated slowly up to 220°. The complete pyrolysis took about six hours. The liquid distilled and condensed in the Dry Ice-acetone trap. The color was deep blue, about like that of the copper-ammonia complex ion. The liquid and solid (about 6 milliliters of water) were removed, separated, washed with dilute hydrochloric acid, dried over Drierite and distilled at atmospheric pressure. The boiling point was 119.5°. The index of refraction was 1.3910 at 29°. The compound was identified as 2-nitropropane, 28 grams, 68% of the theoretical was obtained. Proof of identity is given below:

2-Nitropropane: index of refraction at 29°: 1.3910; boiling point: 119.5°.

Compound obtained: index of refraction at 29°: 1.3910; boiling point: 119.5°. Infrared curves were run on this compound and 2-nitropropane. They were identical.

Water was put into the reaction vessel and allowed to stand overnight to dissolve the other product of decomposition. The next day, the solution was filtered and evaporated on the steam bath. A fair yield of piperidine hydrochloride was recovered and recrystallized from the residue. The crystallizing solvent was methyl isobutyl ketone. The melting point was 244°, the same as for piperidine hydrochloride.

Analysis:	Calculated	Found
	Chloride 29.20%	Chloride 29.80%

Products obtained were 2-nitropropane, piperidine hydrochloride, water and probably carbon dioxide.

Pyrolysis of N-(2-nitro-2-methylpropyl)-morpholine hydrochloride

The hydrochloride salt was prepared by passing gaseous hydrogen chloride through an ethereal solution of N-(2-nitro-2-methylpropyl)-morpholine. The salt was filtered and dried in a vacuum desiccator. The melting point was 173.5°. A quantity of 104 grams (0.46 mole) of the hydrochloride was placed in a 300 milliliter round bottom, one-necked thermometer-well flask fitted with thermometer, heating mantle, Claisen distilling head with water-cooled condenser, receiver and vacuum take-off with cold trap. A safety shield was placed in front of the apparatus before proceeding.

The pressure was reduced to 10 millimeters of Hg. and heating was started. The temperature was elevated slowly. The pyrolysis appeared to begin around 100° and the temperature was gradually increased to 200°. The complete pyrolysis took about five hours. The decomposition at one time was somewhat violent. The liquid distilled and condensed in the Dry Ice-acetone trap. The color again was a deep blue like that of the copper-ammonia complex ion, and the first 2 or 3 milliliters were responsible for the color. The liquid was taken out and separated from the 6 milliliters of water, dried over Drierite, and distilled at atmospheric pressure. The boiling point was 119.5° and the index of refraction 1.3918 at 31°. The compound was identified as 2-nitropropane and a yield of 34 grams 81% of the theoretical was obtained. Proof of identity of 2-nitropropane is given below:

2-Nitropropane: index of refraction at 29°: 1.3910; boiling point: 119.5°.

Compound obtained: index of refraction at 29°: 1.3910; boiling point: 119.5°. Infrared curves were run on this compound and 2-nitropropane. They were identical.

Water was put into the reaction vessel with the charred mass and allowed to stand overnight. The next day the solution was filtered and evaporated on the steam bath. The residue was recrystallized from amyl alcohol, and was found to have a melting point of 174°, the same as that of morpholine hydrochloride. A yield of 25 grams was obtained, 49% of the theoretical.

Products obtained were 2-nitropropane, morpholine hydrochloride, water and probably carbon dioxide.

DISCUSSION

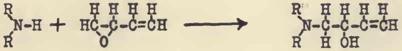
The para-methoxybenzyl alcohol was converted to the chloride in good yield by the method of Quelet and Allard. However, the attempted preparation of para-methoxybenzyl chloride, in a revised method of that given in Organic Syntheses from cheap starting materials, failed to yield any of the halide. A fair yield of di-(para-methoxyphenyl) methane was obtained. This was shown from physical constants, and from the fact that varying percentages of this were formed when the various compounds listed in Organic Syntheses were prepared. It is still believed that the para-methoxybenzyl chloride could be formed by varying the temperature and the time of heating as those were the factors which were varied in preparation of halides described in the above cited reference.

The para-chlorobenzyl chloride and the para-methoxybenzyl chloride were converted respectively to di-(para-chlorobenzyl) amine and di-(para-methoxybenzyl) amine in a fairly satisfactory yield by a method worked out by Butler and Bunch in which they obtained optimum yields of monoamines, diamines, and triamines, by varying the concentrations of the respective alkyl halides and ammonia. Since the starting materials were quite expensive, experiments were not carried out to determine the optimum conditions for the best yield, but instead the concentrations which gave maximum values for similar amines were used. The yield of di-(para-chlorobenzyl) amine was 27% while that for di-(para-methoxybenzyl) amine was 34%. One would expect a better yield for the latter on the basis of an electronic interpretation. The oxygen should release electrons to the ring thus increasing the electron density at the methylene carbon, enabling the chlorine to pull away with greater ease, according to Alexander. The carbonium ion formed is stabilized by resonance until the ammonia molecule moves up with its nucleophilic center. The chlorine in the para position in para-chlorobenzyl chloride withdraws electrons from the ring inductively, thus inhibiting the loss of the chlorine from the molecule. The percentage yield should not be reviewed too critically, however, as the disubstituted amines had very high boiling points at very low pressure, and to avoid appreciable formation of the triamine at the high temperature of distillation, it was necessary to sacrifice yield by washing the hydrochloride form with ethyl alcohol to remove the unused halide and the monoamine hydrochloride.

In trial preparations where the para-chlorobenzyl chloride, and para-methoxybenzyl chloride were not washed from their respective disubstituted amines before distillation, a fair amount of the substituted benzyl chloride was recovered, and an appreciable quantity of a very high boiling liquid was left in the distillation flask. In the reaction with para-chlorobenzyl chloride and ammonia, the residue upon cooling solidified, was recrystallized, and analyzed. The analysis showed it to be tri-para-chlorobenzylamine. The residue from the para-methoxybenzylamine distillation was recrystallized, but due to insufficient time was not analyzed. Information from physical constants, solubility in ether, etc., indicated it was tri-methoxybenzylamine. This seems to indicate a method for the preparation of tri-substituted benzylamines.

The dibenzylamine, the di-(para-chlorobenzyl) amine, and the di-(para-methoxy)-benzylamine were converted to their corresponding 1-diamino-2-hydroxybutene-3 compounds in a manner similar to that of Kerwin, Ullyot, Fuson, and Zirckle by reacting the disubstituted amine with 3,4-epoxybutene-1. The reason for maintaining the temperature at 90°-95° for a while was to allow a sufficient amount of reaction to take place as the mixture initially refluxed at this temperature. Afterwards the temperature was elevated to 140° to finish the reaction. The yield of 1-di-benzylamino-2-hydroxy butene-3 was 25% of the theoretical, the di-(para-chlorobenzyl) amino-2-hydroxy butene-3, 24%, and the di-(para-methoxybenzyl) amino-2-hydroxy butene-3, 45%. The di-(para-methoxybenzyl) derivative gave the best yield, the dibenzyl next, and the di-(para-chlorobenzyl) compound, least. Although there was little difference in the percentage yield of the last two, the per centage yields were in the order again, that one would predict on the basis of an electronic intrepretation. The oxygen of the methoxy group should release electrons to the ring thus resulting in a greater electron density around the nitrogen, causing it to be more basic than dibenzylamine, and thus attack the positive center of the epoxy molecule. The chlorines in the para positions of di-(para-chlorobenzyl) amine should withdraw electrons inductively from the rings causing the electron density around the nitrogen to be less, and thus result in a weaker base than dibenzylamine.

The epoxy ring opens in such a manner as to give the amino group the number one position on the chain, and the hydroxy group appears on the second carbon. Only in those cases of compounds in which the R groups are very small have there been reports of the epoxy ring opening to give



$$\mathrm{R_2N{-}H + H_2\underset{\diagdown O \diagup}{C{-}C}H{-}CH{=}CH_2 \longrightarrow R_2N{-}CH_2{-}CH(OH){-}CH{=}CH_2}$$

such a linkage on the second carbon. Ammonia, for example, has been shown to open the ring in this way in some cases.

The hydrochlorides of these compounds were prepared, but they were difficult to recrystallize in a nice crystalline form since they seemed to absorb impurities and were spongy-like. The hydrochloride of the dibenzylamine derivative was reported previously as a hygroscopic compound precipitated from ether and hydrogen chloride gas. However, if it is precipitated from benzene with the gaseous hydrogen chloride and washed quickly with acetone soon after the crystals form, it can be obtained as a dry white crystalline solid. If precipitated from ether and recrystallized, it tends to appear as a spongy mass each time.

The para-methoxybenzyl derivative distilled over in syrupy strings similar to egg white dripping from the condenser. The hydrochloride precipitated from ether as a viscous material on the walls of the container, and it took several days for the substance to become crystalline. Apparently, some time is required for the very large molecules to align themselves in crystalline form. The proof of the 1-dibenzylamino-2-hydroxybutene-3 hydrochloride was taken from physical constants since it was prepared previously. The other two were analyzed with the per centage composition of nitrogen and chlorine agreeing very closely with the theoretical value.

The 1-dibenzylamino-2-hydroxy butene-3 hydrochloride was converted to 1-dibenzylamino-2-chlorobutene-3 hydrochloride by reacting it with thionyl chloride. The product was very syrupy and after a number of trials it was discovered that if the solvent was removed right away, evacuated in a desiccator for a while and washed with methyl isobutyl ketone to remove some of the resin-like material, it could be recrystallized from ethanol to give a white crystalline solid. The same end product was obtained by reacting the starting material with phosphorus pentachloride in a procedure similar to the one above. The product was perhaps a little easier to purify from the phosphorus pentachloride reaction. The compound was shown to be 1-dibenzylamino-2-chlorobutene-3 hydrochloride from the analysis since the results of nitrogen and chloride analyses agreed quite well with the theoretical value.

The di-(para-chlorobenzyl) amino-2-hydroxy butene-3 hydrochloride conversion to the 2-chloro derivative by the use of thionyl chloride was attempted without success. The new product obtained gave an analysis greatly different from that of the one expected. A compound with the same melting point was obtained by using phosphorus pentachloride on the amino alcohol hydrochloride.

The attempted conversion of the di-(para-methoxybenzyl) amino-2-hydroxy butene-3 hydrochloride to the corresponding 2-chloro derivative failed due to the fact that no crystalline solid could be obtained from the viscous liquid even after evacuation. Crystals were observed in the residue but it was not possible to isolate them.

The viscous nature of the crude product in all three cases appeared to be linked to the electronic structure as the para-chloro compound was the easiest to manipulate and the para-methoxy derivative was the most difficult.

Beta-nitroamines of the type used in this study were readily prepared by reaction of the appropriate secondary amine with formaldehyde and 2-nitropropane. Because of the monofunctional nature of 2-nitropropane, the compounds studied were prepared from this nitroalkane. The compounds prepared were N-(2-nitro-2-methylpropyl)-diethylamine, N-(2-nitro-2-methylpropyl)-piperidine, N-(2-nitro-2-methylpropyl)-morpholine, N-(2-nitro-2-methylpropyl)-dibutylamine, N-(2-nitro-2-methylpropyl)-dipropylamine, and N-(2-nitro-2-methylpropyl)-diallylamine.

These compounds were reacted with equimolar quantities of each of the following: methyl iodide, benzyl chloride, allyl bromide, and ethyl iodide.

Of the above listed compounds, the following reacted with methyl iodide to give products which were isolated in crystalline form: N-(2-nitro-2-methylpropyl)-diethylamine, N-(2-nitro-2-methylpropyl)-piperidine, N-(2-nitro-2-methylpropyl)-morpholine, and N-(2-nitro-2-methylpropyl)-diallylamine. In each case where it was possible to obtain the product in crystalline form, the methyl quaternary ammonium iodide was formed. The salts were analyzed for ionizable iodides and all gave results very close to the theoretical amounts. These results were not too surprising since most tertiary amines in their reactions with methyl iodide retain the methyl group and form the iodide salt.

The rate of reaction from the quantity of product formed was observed to take place in the following order: the piperidine derivative, first; the diethyl derivative, second; the morpholine derivative, third; and the diallyl derivative, fourth.

With benzyl chloride, the following reacted to give products which were isolated in crystalline form: N-(2-nitro-2-methylpropyl)-diethylamine, N-(2-nitro-2-methylpropyl)-piperidine, and N-(2-nitro-2-methylpropyl)-morpholine. The rates of reaction were: the piperidine derivative, first; the diethyl and morpholine derivatives about the same rate.

In this series, the 2-nitro-2-methylpropyl group was lost in each case, and benzyl-piperidine hydrochloride, benzyl diethylamine hydrochloride, and benzyl morpholine hydrochloride were formed respectively. These results were obtained by analysis for ionizable chloride in which ~~whereby~~ all agreed very closely with the theoretical amount. It was noted that the 2-nitro-2-methylpropyl group split off in the formation of the new compound.

In the allyl bromide series, N-(2-nitro-2-methylpropyl)-diethylamine, N-(2-nitro-2-methylpropyl)-piperidine, N-(2-nitro-2-methylpropyl)-morpholine, N-(2-nitro-2-methylpropyl)-dibutylamine, and N-(2-nitro-2-methylpropyl)-dipropylamine reacted to give products which were obtained in crystalline form. This group of compounds was somewhat more difficult to recrystallize than any of the other groups of the Mannich bases. This was in accord with previous work done in this laboratory[28,29,30] with allyl type quaternaries. Various solvents were used to wash out the resinous material to aid in recrystallization. Again the rate of reaction was with the piperidine derivative, first; the diethyl derivative a close second; and the others were too slow to differentiate between them.

In this series, the hydrobromides, the 2-nitro-2-methylpropyl derivatives of piperidine, diethylamine and morpholine were formed, the allyl group being lost. The dibutyl and the dipropyl derivatives lost both the allyl and the 2-nitro-2-methylpropyl groups and resulted in final products of dibutylamine hydrobromide and dipropylamine hydrobromides.

Pyrolyses of the hydrochlorides of the N-(2-nitro-2-methylpropyl)-diethylamine, N-(2-nitro-2-methylpropyl)-piperidine, and N-(2-nitro-2-methylpropyl)-morpholine were carried out by decomposing them at 10 mm. of Hg. pressure. The temperature depended upon the particular compound, but in general, decomposition began around 100° and was continued to slightly over 200°. Some of the decompositions proceeded quite rapidly once they were well started, so it was necessary to use a safety shield as a precaution.

In each pyrolysis, 2-nitropropane was one of the decomposition products and was obtained up to 81% of the theoretical yield. This was established from the boiling point, the index of refraction, and from infrared curves. The curves were identical to the one from 2-nitropropane. Diethylamine hydrochloride, piperidine hydrochloride, and morpholine hydrochloride was obtained from the decomposition residue from their respective salts. Each was analyzed and agreed very closely with the theoretical amount for its respective hydrochloride. Physical constants also agreed with literature values. The yields of the hydrochlorides varied from small values up to 48% of the theoretical value. This was not surprising considering the tar-like, charred mass left in the flask. Water was another product obtained in fair yield in each case along with an odor of formaldehyde. No nitropropene was obtained in any of the pyrolyses as was possibly expected.

It was noticed that in the reactions of the Mannich bases with the alkyl halides, the general order of reaction was: piperidine derivatives first, the diethyl derivatives second, and morpholine derivatives third.

From the recrystallization of these tertiary and quaternary ammonium halides, it appeared that some of the compounds could be easily recrystallized, while some needed to be washed with selective solvents to remove resinous material before crystallization was begun. After such washing, crystalline compounds could be obtained by repeated recrystallization. For example, upon dissolving some of these solids in a particular solvent, it appeared that the resinous material had all gone into solution, but upon recrystallization, the impurity absorbed quickly on the crystals. It was observed that many of the compounds were hygroscopic only when they had absorbed small amounts of these impurities, and if they were washed with selective solvents to remove these impurities, non-hygroscopic crystals were obtained.

SUMMARY

Para-methoxybenzyl alcohol was converted to the chloride in good yield. Para-chlorobenzyl chloride and para-methoxybenzyl chloride were reacted with calculated concentrations of ammonia. The corresponding disubstituted amines were produced in fairly satisfactory yield. The relative yields obtained were as one would have predicted from electronic structure.

Benzyl, di-para-chlorobenzyl, and di-para-methoxybenzyl derivatives of 2-hydroxybutene-3 were produced in fairly satisfactory yield by reacting the disubstituted amines with 3,4-epoxybutene-1. The relative yields again were in the order predicted on an electronic basis. The hydroxy compounds were reacted with thionyl chloride. The dibenzyl derivative reacted to give the corresponding chloro derivative. The di-para-chlorobenzyl derivative gave a product which could not be identified while the di-para-methoxy derivative could not be claimed from the syrup-like mixture in the reaction flask.

The Mannich reaction was used to prepare a number of beta-nitro compounds which were of interest in this study. Then they were reacted with methyl iodide, benzyl chloride, allyl bromide, and ethyl iodide. The product formed with methyl iodide in each case was the methyl

quaternary ammonium iodide of the original tertiary amine. Benzyl chloride reacted in such a way as to split off the 2-nitro-2-methylpropyl group to form the benzyl hydrochloride of ethylamine, morpholine, and piperidine. Allyl bromide reacted in such a way that the hydrobromides were formed with the 2-nitro-2-methylpropyl derivatives of piperidine, diethylamine, and morpholine. The dipropyl and dibutyl derivatives lost their 2-nitro-2-methylpropyl groups to give dipropylamine hydrobromide and dibutylamine hydrobromide respectively. In the one reaction with ethyl iodide in which crystalline material was obtained, the hydroiodide of the starting tertiary amine was obtained. The piperidine derivative appeared to be the most reactive with each of the halides.

In the pyrolyses of the hydrochlorides of the Mannich bases, 2-nitropropane, water, and the corresponding disubstituted amines were obtained in good yield.

Crystallization was continually a problem, but with the use of selective solvents to wash out resinous materials before recrystallization began, it was possible in many cases to obtain nice crystalline products.

BIBLIOGRAPHY

(1) Ullyot, J. Am. Chem Soc. 72, 940-2 (1950).

(2) Loew, Achenbach, and Micetich, J. Pharmacol Exptl. Therop. 97, 441 (1949).

(3) Loew and Micetich, J. Pharmacol. Exptl. Therop. 94, 339-49 (1948).

(4) Gump and Nikowitz, J. Am. Chem. Soc. 72, 1309-12 (1950).

(5) Nickerson, J. Pharmacol. Exptl. Therop. 95, Part II 40 (1949).

(6) Nickerson and Gump, J. Pharmacol. Exptl. Therop. 97, 25 (1949).

(7) Loew and Micetich, J. Pharmacol. Exptl. Therop. 93, 434 (1948).

(8) Loew and Micetich, J. Pharmacol. Exptl. Therop. 95, 448 (1949).

(9) Garbrecht, Hunter, and Wright, J. Am. Chem. Soc. 72, 1359 (1950).

(10) Hunt, J. Pharmacol. Exptl. Therop. 95, 177-184 (1949).

(11) Bartlett, Rose, and Swain, J. Am. Chem. Soc. 69, 2971 (1947).

(12) Hunt, J. Am. Chem. Soc. 69, 2961 (1947).

(13) Mannich, Arc. Pharm. 250, 647 (1912).

(14) Henry, Berichte 28, 381 (1895).

(15) Bodendorf and Koralewski, Arch. Pharm. 271, 101 (1933).

(16) Rowland Laboratories, 1330 Talleyrand Avenue, Jacksonville, Florida.

(17) Geller Microanalytical Laboratories, 215 W. 101 St., New York, N.Y.

(18) Quelet and Allard, Bull. Soc. Chim. (5) 4, 1468-72 (1937).

(19) Butler and Benjamine, J. Chem. Educ. 28, 191 (1951).

(20) Kerwin, Ullyot, Fuson, and Zirckle, J. Am. Chem. Soc. 69, 2961 (1947).

(21) Kadesch, J. Am. Chem. Soc. 68, 44 (1946).

(22) Senkus, J. Am. Chem. Soc. 68, 10 (1946).

(23) Johnson, J. Am. Chem. Soc. 68, 12 (1946).

(24) Vavon, Bolle, and Calin, Bull. Soc. Chim. (5) 6, 1025 (1939).

(25) Beck, Ann. 194, 323 (1878).

(26) Rupe and Brentons, Helv. Chem. Acta. 588-96 (1936) C.A. 30, 4842 (1936).

(27) Winnan, J. Am. Chem. Soc. 61, 3564-5 (1939).

(28) R. L. Goette, Ph.D. Dissertation, University of Florida, p. 54 (1953).

(29) R. L. Bunch, Ph.D. Dissertation, University of Florida, p. 20 (1949).

(30) R.J. Angelo, Master's Thesis, University of Florida, p. 24 (1953).

BIOGRAPHICAL ITEMS

Carl I. Michaelis was born at Paxico, Kansas, on May 11, 1918. He attended the parochial grade school, and was graduated from Paxico High School in 1936. He entered the University of Kansas in 1941, and was graduated in 1945 with the degree of Bachelor of Arts. During the following summer he worked at the Kansas State Plastics Laboratory in Lawrence, Kansas. He was awarded a graduate assistantship and entered Graduate School at the University of Kansas in 1945 and received the degree Master of Arts two years later. Following this, he took a position as Instructor of Chemistry at Florida State University where he taught for three years.

In 1950 he entered the Graduate School of the University of Florida. During the first year and a half at the University of Florida, Mr. Michaelis was employed as a teaching assistant; the last year and a half he was employed as Instructor.

Mr. Michaelis is a member of Sigma Xi, Alpha Chi Sigma, Gamma Sigma Epsilon, honorary chemical fraternity, the American Chemical Society, the American Association of University Professors, and the John Henry Newman Honorary Society.

COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

August 10, 1953.

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